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Does high dose vitamin D supplementation enhance cognition?: A randomized trial in healthy adults

Jacqueline A Pettersen *

Northern Medical Program, University of Northern British Columbia, Prince George, Canada
Division of Neurology, Department of Internal Medicine, University of British Columbia, Vancouver, Canada

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ABSTRACT

Background: Insufficiency of 25-hydroxyvitamin D [25(OH)D] has been associated with dementia and cognitive decline. However, the effects of vitamin D supplementation on cognition are unclear. It was hypothesized that high dose vitamin D3 supplementation would result in enhanced cognitive functioning, particularly among adults whose 25(OH)D levels were insufficient (<75 nmol/L) at baseline.
Methods: Healthy adults ($n = 82$) from northern British Columbia, Canada (54° north latitude) with baseline 25(OH)D levels ≤100 nmol/L were randomized and blinded to High Dose (4000 IU/d) versus Low Dose (400 IU/d) vitamin D3 (cholecalciferol) for 18 weeks. Baseline and follow-up serum 25(OH)D and cognitive performance were assessed and the latter consisted of: Symbol Digit Modalities Test, verbal (phonemic) fluency, digit span, and the CANTAB® computerized battery. Results: There were no significant baseline differences between Low ($n = 40$) and High ($n = 42$) dose groups. Serum 25(OH)D increased significantly more in the High Dose (from 67.2 ± 20 to 130.6 ± 26 nmol/L) than the Low Dose group (60.5 ± 22 to 85.9 ± 16 nmol/L), $p = 0.0001$. Performance improved in the High Dose group on nonverbal (visual) memory, as assessed by the Pattern Recognition Memory task (PRM), from 84.1 ± 14.9 to 88.3 ± 13.2, $p = 0.043$ (d = 0.3) and Paired Associates Learning Task, (PAL) number of stages completed, from 4.86 ± 0.35 to 4.95 ± 0.22, $p = 0.044$ (d = 0.5), but not in the Low Dose Group. Mixed effects modeling controlling for age, education, sex and baseline performance revealed that the degree of improvement was comparatively greater in the High Dose Group for these tasks, approaching significance: PRM, $p = 0.11$ (d = 0.4), PAL, $p = 0.058$ (d = 0.4). Among those who had insufficient 25(OH)D (<75 nmol/L) at baseline, the High Dose group ($n = 23$) improved significantly ($p = 0.005$, d = 0.7) and to a comparatively greater degree on the PRM ($p = 0.025$, d = 0.6).
Conclusions: Nonverbal (visual) memory seems to benefit from higher doses of vitamin D supplementation, particularly among those who are insufficient (<75 nmol/L) at baseline, while verbal memory and other cognitive domains do not. These findings are consistent with recent cross-sectional and longitudinal studies, which have demonstrated significant positive associations between 25(OH)D levels and nonverbal, but not verbal, memory. While our findings require confirmation, they suggest that higher 25(OH)D is particularly important for higher level cognitive functioning, specifically nonverbal (visual) memory, which also utilizes executive functioning processes.

Vitamin D insufficiency, which has been estimated to affect one billion people worldwide (Holick, 2007), has been implicated in cognitive impairment and dementia. In addition to vitamin D receptors and 1, α-hydroxylase (the enzyme that catalyzes the conversion to calcitriol, the active form of vitamin D from the immediate precursor 25-hydroxycholecalciferol). being co-located in the brain (McCann and Ames, 2008), vitamin D also increases acetylcholine levels (Sonnenberg et al., 1986), and hippocampal neuron densities (Landfield and Cadwallader-Neal, 1998), decreases proinflammatory cytokines (Schleithoff et al., 2006), enhances neuroprotection (Brewer et al., 2001) and augments amyloid-β clearance (Massoumi et al., 2009), processes importantly implicated in age-related cognitive decline and dementia. Meta-analyses of cross-sectional studies have reported impaired cognitive function among individuals with insufficient levels (Balion et al., 2012; Etgen et al., 2012) while analyses of longitudinal studies revealed an increased odds of 2.5 (95% confidence interval 1.74–3.56), $p < 0.0001$ of incident cognitive impairment (Etgen et al., 2012) and a 20% increased risk of developing Alzheimer's (Shen and Ji, 2015). Further, analyses of case

* Northern Medical Program, University of Northern British Columbia, 3333 University Way, Prince George, British Columbia V2N 4Z9, Canada.
E-mail address: pettersj@unbc.ca.

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control studies found vitamin D levels (assessed as serum levels of 25(OH)D) to be 6–15 nmol/L lower in Alzheimer's patients compared to age-matched controls (Balion et al., 2012).

While vitamin D supplementation enhances cognition and improves markers of pathology in rodent models of Alzheimer's disease (Yu et al., 2011; Taghizadeh et al., 2014) and aging (Latimer et al., 2014), there has been a dearth of randomized control supplementation trials in humans. The only published trial involving individuals with Alzheimer's (Stein et al., 2011) enrolled 32 subjects with mild-moderate disease and baseline 25(OH)D levels <90 nmol/L. Following an eight-week run-in of 1000 IU/d of vitamin D2, they were randomized to either 7000 IU/d or continued on 1000 IU/d for eight weeks. Mean post-treatment 25(OH)D levels were 187 nmol/L and 72 nmol/L, respectively. No significant differences were found between the two groups on the ADAS-cog (a measure of global cognition), the Disability Assessment for Dementia (DAD) scale (a measure of functional abilities), nor the Logical Memory subscale of the Wechsler Memory Scale (a measure of verbal memory). There have been three published studies to date involving middle-aged to older individuals without dementia (Corless et al., 1985; Dhesi et al., 2004; Rossom et al., 2012), and one involving young adults (Dean et al., 2011). In one study, elderly hospitalized individuals ($N = 82$) with insufficient 25(OH)D levels at baseline (<40 nmol/L) were treated with 9000 IU/d of vitamin D2 or placebo for 40 weeks (Corless et al., 1985). There was no significant improvement on a limited test of cognition. In contrast, Dhesi et al. (2004) demonstrated significant improvement on a choice reaction time task at six months among vitamin D deficient (<30 nmol/L) elderly individuals, prone to falling, treated with a single 600,000 IU injection of vitamin D2 as compared to those given placebo. A post-hoc analysis of the Women's Health Initiative Study (Rossom et al., 2012) did not reveal any effect on cognition among women treated with low dose vitamin D3 (400 IU/d) along with calcium (1000 mg/d) over eight years. However, subsequent vitamin D levels were not obtained, and adherence to study supplementation was reported to be poor. Among 128 young adults (mean age 22 years), daily supplementation of 5000 IU vitamin D3 versus placebo for 6 weeks did not result in significant cognitive improvement, as assessed by executive functioning tests and psychiatric measures.

Inconsistent and/or null results from these randomized trials can possibly be attributed to a number of methodological issues, some of which have been previously commented upon (Annweiler and Beauchet, 2011; Annweiler and Beauchet, 2013; Landel et al., 2016). In particular, the duration of supplementation may have been too short in some of these studies since the effects of vitamin D supplementation on some outcomes can take as long as 16 weeks or more to occur after initiating supplementation (Annweiler and Beauchet, 2011), such as changes in muscle function (Annweiler et al., 2010). These studies are also lacking in the use of comprehensive cognitive measures assessing cognitive domains importantly affected in aging and in dementia, including executive functioning, which has been most consistently associated with vitamin D status in observational studies (Annweiler et al., 2013). Only one trial (e.g., Stein et al., 2011) used a recognized test of verbal memory but none assessed non-verbal memory. The form and dose of vitamin D is likely also important. Some authorities suggest that vitamin D2, which was used in three of the five trials, is not as potent or as bioavailable as D3 (Armas et al., 2004; Roth et al., 2008) and that, as in the Women's Health Initiative Study (Rossom et al., 2012), a dose of vitamin D3 as low as 400 IU/d, which is below the current recommended daily intake (Ross et al., 2011), may be too low to exert a measurable effect on cognition. Further, the addition of calcium in this trial has been critiqued as possibly negating any possible benefits that vitamin D may have had (Annweiler and Beauchet, 2013). Relatively low levels of compliance with supplementation and the absence of post-assessment 25(OH)D levels have been cited as other potential issues. Finally, it has been suggested by Landel et al. (2016) that vitamin D supplementation may not benefit cognition in those who already have sufficient levels at baseline. Similarly, it may be less likely to benefit those who already have high-level stable cognitive functioning. For example, a trial involving young adults, mostly university students from Australia (Dean et al., 2011), did not find any benefits to supplementation and only 10 of 128 participants had insufficient levels at baseline. "Insufficiency" has been variously defined as <50 nmol/L by some authorities, including the Institute of Medicine (Ross et al., 2011), and <75 nmol/L by other authorities, including the Endocrine Society (Holick et al., 2011). Importantly, these cut-off values have been largely based on skeletal outcomes and to date, the optimal level for cognition is not known.

The present study sought to determine whether vitamin D supplementation, improves cognition in adults free of dementia, taking into account the methodological issues discussed above, including supplementing with a reasonably high dose (i.e., 4000 IU/d versus 400 IU/d) of vitamin D3, rather than D2, for a duration of several weeks, with baseline and post-treatment 25(OH)D levels obtained, and assessing a range of cognitive domains, including executive functioning/working memory, verbal and non-verbal memory, attention, and components of language. Participation was not limited to those considered to have insufficient levels of 25(OH)D (defined in this study as <75 nmol/L), but rather, those with levels as high as 100 nmol/L were included and a predetermined subgroup analysis was also planned, assessing just those individuals with lower levels at baseline. It was hypothesized that high dose vitamin D3 supplementation would result in enhanced cognitive functioning, particularly among whose 25(OH)D levels were insufficient (<75 nmol/L) at baseline.

1. Methods

1.1. Study design

This was an 18-week, randomized trial in healthy adults to evaluate the effects of high dose (4000 IU/d) vitamin D3 (cholecalciferol) on cognition, as assessed by a battery of cognitive tests covering a number of cognitive domains. The comparator group received low dose (400 IU/d) of cholecalciferol. Allocation to treatment group was 1:1.

1.2. Participants

Participants consisted of healthy adults from Northern British Columbia, Canada (54° N) who had responded to advertisements posted in the newspaper, at the local university and college, three seniors' centers, the hospital, and several local family physicians' offices. Inclusion criteria included age over 20 years, and English literacy. Exclusion criteria included visual or auditory impediments that would limit completion of the cognitive tests, dementia, history of brain tumor, brain injury, or symptomatic stroke. Participants included in the randomized trial were drawn from those who had participated in the observational component of one of two related studies: DCOG or DCOG2 (Pettersen et al., 2014; Pettersen, 2016) and who had a baseline 25(OH)D level of ≤100 nmol/L. Use of supplements (vitamin D and/or calcium) was otherwise not a contraindication to participation but participants were instructed to maintain the same doses throughout the study. All participants provided written informed consent. The study protocol was approved by the University of British Columbia, the University of Northern British Columbia, and the Northern Health Authority research ethics committees. As this study was confined to time limits (i.e. all participants enrolled in the winter and early spring months), the final sample size was based on one of convenience. However, assuming 2-sided $\alpha = 0.05$, power of 80%, and a moderate effect size of Cohen's d between 0.50 and 0.60, a sample size of approximately 40–60 participants per group would be required.